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Small Dense LDL - The real culprit - A review article

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ABSTRACT
Atherosclerosis is an insidious disease of pluricasual etiology. Although the atherogenic risk attributed to elevated plasma LDL cholesterol , is well beyond the dispute, there is considerable overlap in the distribution of plasma cholesterol levels between healthy subjects and in patients with documented CHD. Because the classical lipid risk factors by no means perfectly predict CHD in patients, lipoprotein subfractionation has the potential to improve risk prediction. The objective of the present article is to critically discuss in brief about the overall review of small- dense LDL. A preponderance of small dense LDL is associated with a 3-7 fold increase in CHD risk, independent of LDL concentration. LDL are spherical particles 22-29 nm in diameter, composed of a core of esterified cholesterol and triacylglycerol, a surface lipid coat of unesterified cholesterol and phospholipid. Key to understanding the metabolic conditions that led to the generation of small- sized LDL particles is the observation that appear in individuals who are hypertriglyceridemic and have a low concentration of HDL. Small dense LDL particles are most frequently part of a complex plurimetabolic syndrome. Measurement of LDL particle size may be of benefit for cardiovascular risk stratification as an adjunct to routine cholesterol testing and global risk assessment for selected populations. The burden of proof for any newly proposed risk factor is that it must add significantly to risk assessment by existing measurements, or that is equivalent but more economical. LDL subclassification does not meet either of these expectations. Fulillment of these expectations will represent a considerable challenge, but additional major developments in this area may represent significant leaps in preventive cardiology.

Key words: Small dense LDL, hpertriglyceridemia, Coronary heart disease, atherosclerosis.

INTRODUCTION

Atherosclerosis is an insidious disease of pluricasual etiology. Growth of atherosclerotic plaque does not occur in smooth linear fashion , but rather discontinuously with periods of relative quiescence punctuated by periods of rapid evolution.

Accumulation of cholesterol in the arterial intima may link mechanistically with leukocyte recruitment, a key event in the atherosclerotic lesion formation. Is cholesterol the culprit? Although the atherogenic risk attributed to elevated plasma cholesterol , is well beyond the dispute, there is considerable overlap in the distribution of plasma cholesterol levels between healthy subjects and in patients with documented CHD**[1].**
Cholesterol is a participant, not the cause of cardiovascular disease. The major lipoprotein types, very low-density lipoprotein (VLDL) , low- density lipoprotein (LDL) and high- density lipoprotein (HDL) are composed of many subgroups**[2]** .Because the classical lipid risk factors by no means perfectly predict CHD in patients, lipoprotein subfractionation has the potential to improve risk prediction. A number of studies suggest that the potential atherogenecity of LDL may be related to specific LDL- subpopulations **[3,4,5]** . The objective of the present article is to critically discuss in brief about the overall review of small- dense LDL.

CHARACTERISTICS AND FORMATION

LDL are spherical particles 22-29 nm in diameter, composed of a core of esterified cholesterol and triacylglycerol, a surface lipid coat of unesterified cholesterol and phospholipid. The size of an LDL particle depends on how much is in the core and the lipid content naturally determines its density. Thus smaller LDL is denser, larger LDL is lighter. Seven distinct LDL subpopulations were resolved by density-gradient ultracentrifugation and polyacrylamide – gradient gel electrophoresis**[6]** .

The size of the predominant LDL particle determines the classification : 22-25.5nm is small , 25.5 to 26.5nm is intermediate and 26.5-28.5nm is large. Austin et al **[7]** identified two subclass pattern : the classical category – pattern A is more than 25.5nm and pattern B is 25.5nm or less.

Small dense LDL may be formed by metabolic channeling of large VLDL**[8]** , lipolysis of intermediate density lipoprotein and large LDL by hepatic lipase**[9,10]** ,remodelling of LDL by cholesterol ester transfer protein (CETP) secretion into the plasma by liver or a combination of these processes. Key to understanding the metabolic

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conditions that led to the generation of small-sized LDL particles is the observation that appear in individuals who are hypertriglyceridemic and have a low concentration of HDL.

METHODS USED FOR MEASURING SMALL - DENSE LDL -

Analytical ultracentrifugation is the original gold standard method. It measures the flotation velocity of LDL in a gravitational field. Preparative ultracentrifugation seperates discrete LDL subfractions. Gradient gel electrophoresis is a simple readily available method to determine LDL size . Nuclear Magnetic Resonance measures the diameter and lipid concentration of LDL **[11] .**

EPIDEMOLOGY –

There is now a wealth of evidence from cross-sectional and prospective studies to show that LDL particle size is significantly associated with CHD and predictive of increased coronary risk. A preponderance of small dense LDL is associated with a 3-7 fold increase in CHD risk, independent of LDL concentration **[12, 13]** .Small dense LDL was also found to be elevated in patients with diabetes, renal disease and other disorders such as pre- eclampsia **[14 - 16]**.

MECHANISMS OF ATHEROGENICITY FOR LDL SUBFRACTIONS –

Mechanistic support for small LDL having a special atherogenicity depends on atherogenic actions being greater for small than for intermediate or large LDL. This subfraction binds less well to the LDL receptor in comparison with its larger counterparts**[17]** , which has the consequence of prolonging its lifetime in the circulation. Conversely, the particles appear to interact more strongly with arterial wall proteoglycans**[18]**.

There is as yet no clear explanation for this preferential binding of small dense LDL to proteoglycans, although the exposure of basic amino acids and positive charge on the surface of small dense LDL must influence binding to these highly- electronegative proteoglycans to some degree. In the ‘‘response to retention’’ hypothesis of atherosclerosis, this property will increase the time that lipoprotein spends trapped in the subendothelial space of the arterial wall, hence increase the opportunity to promote atherogenic changes. It is likely that these altered functions are the result of apoB in small dense LDL adopting a conformation different from that in larger LDL species, which favours proteoglycan binding but inhibits receptor- mediated catabolism **[19]**.

In addition, it has been reported that small dense LDL is the most readily oxidized subfraction in the lipoprotein class**[20]**. Oxidised LDL is known to cause stimulation of foam cell formation and activation of inflammation. Together these events have formed the mechanistic backbone for the role of small dense LDL in atherogenesis for the last decade.

Rather, it is most likely that small dense LDL phenotype is an important component of a “ minestrone soup” of pro-atherothrombotic abnormalities and that smaller and cholesterol depleted LDL particles exacerbate the risk of CHD when accompanied by other components of the atherogenic dyslipidemia of insulin resistance.

Table : 1) Metabolic abnormalities commonly found among subjects with small dense LDL particles**[8]** -

Abdominal obesity
Hypertriglyceridemia
Low HDL
Increased cholesterol/ HDL ratio
Normal or marginally elevated LDL
Insulin resistance
Hyperinsulinemia
Glucose intolerance and type – 2 diabetes
Elevated fibrinogen and PAI-1 levels
Altered endothelial reactivity

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PHARMACOLOGICAL REGULATION OS SMALL DENSE LDL -

Correction of the hypertriglyceridemic state is an obvious way to lower the probability of the formation of small dense LDL. Fibrates have been shown to be highly successful agents in lowering the plasma concentration of small dense LDL. The compounds are agonists for specific nuclear receptors, and alter the expression of a number of key genes involved in lipoprotein metabolism. Apo C (3) is decreased, while lipoprotein lipase is increased. Both of these effects will accelerate the clearance of VLDL from circulation and as a consequence, reduce plasma levels of s-LDL. Often however the total LDL concentration of patients on fibrates is unaltered.

For the LDL subfraction to shift from a preponderance of small dense LDL(pattern B) to a more normal profile, plasma triglyceride levels must be reduced below the threshold of 1.5mmol/L. The ability to change the LDL subfraction distribution is more evident for compounds such as atorvastatin and rosuvastatin **[19] .**

EFFECT OF DIET AND WEIGHT LOSS ON LDL SUBTYPES -

Low fat, high carbohydrate diets compared with high saturated fat decrease the mean LDL size **[21]** .Weight loss is also associated with a significantly greater decrease in small, dense LDL subclass 3b in pattern B relative to pattern A men **[22]**.

CONCLUSION -

Despite a considerable wealth of evidence to implicate serum cholesterol in atherosclerosis, there is a mis-conception that raised levels of LDL cholesterol represent the most common atherogenic stimulus. The greatest source of lipid- mediated cardiovascular risk still arises from LDL, but as a result of its small size, and increased density and particle number rather than its cholesterol content. Small dense LDL particles are most frequently part of a complex plurimetabolic syndrome. Measurement of LDL particle size may be of benefit for cardiovascular risk stratification as an adjunct to routine cholesterol testing and global risk assessment for selected populations. The burden of proof for any newly proposed risk factor is that it must add significantly to risk assessment by existing measurements, or that is equivalent but more economical. LDL subclassification does not meet either of these expectations. Fulillment of these expectations will represent a considerable challenge, but additional major developments in this area may represent significant leaps in preventive cardiology.

REFERENCES

[1] B.Laarche, T.Lemieux et al. The small dense LDL phenotype and risk of coronary heart disease. Epidemiology; pathophysiology and therapeutic aspects. Diabetes and metabolism 1999 , 25 : 199-211.

[2] Krauss R.M, Burke D.J. Identification of multiple subclasses of plasma low density lipoproteins in normal humans. Journal of Lipid Research.1982, 23 : 93-104.

[3] Berneis K, Jeannert C, Muser J,Felix B,Miserez AR. Low-density lipoprotein size and subclasses are markers of clinically apparent and non-apparent atherosclerosis in type 2 diabetes. Metabolism-clinical and Experimental 2005; 54(2): 227-234.

[4] Natalia Sancho ,Fransisco V,Esteben G et al. Observational study of lipid profile and LDL particle size in patients with metabolic syndrome. Lipids in Health Disease.2011, 10 : 162.

[5] Arsenault B J, Lemieux I, Despress J P, Wareham N J,Luben R,Kastelein J J, Khaw K T, Boekholdt S M. Cholesterol levels in small LDL particles predict the risk of coronary heart disease in the EPIC- Norfolk prospective population study. European Heart Journal 2007; 28 : 2770-2777.

[6] Chung M, Lichtenstein A H, Lau J, Balk E M. Comparability of methods for LDL subfraction determination : A systematic Review. Atherosclerosis. 2009, 205(2) : 342-348.

[7] Austin M.A, Krauss R.M,. Genetic control of low-density lipoprotein subclasses. Lancet (1986)2 : 592 -595.

[8] Packard C J, Gaw A, Demant T, Sphepherd J .Development and application of multicompartmental model to study low density lipoprotein subfraction metabolism. J Lipid Research 1995, 36: 172-187.

[9] Zambon A, Hokanson J E, Brown B G, Brunzell J D. Evidence for a new pathophysiological mechanism for coronary artery disease regression: hepatic lipase mediated changes in LDL density. Circulation 1999: 1959-1964.

[10] Carr M C , Ayyobi A F et al. Contribution of hepatic lipase, lipoprotein lipase and cholesteryl ester transfer protein to LDL and HDL heterogeneity in healthy

women. Atherosclerosis Thrombo Vas Biol 2002: 22; 667-673.

[11] Otvos J D Measurement of lipoprotein subclass profiles by nuclear magnetic resonance spectroscopy. In : Rifai, N, Warnick G R, Dominiczak M H, eds. Handbook of lipoprotein testing.2nd Edition.Washington D C : AACC Press ; 609-623.

[12] Griffin B A, Freeman D J, Tait G W et al..Role of plasma triglyceride in the regulation of plasma low density lipoprotein(LDL) subfractions: relative contribution of small dense LDL to coronary artery disease risk . Atherosclerosis 1994:106; 241-253.

[13] Berneis K K, Krauss R M et al.2002.Metabolic origins and clinical significance of LDL heterogeneity. J Lipid Research 43 : 1363-1379.

[14] Richard W Nesto.LDL cholesterol lowering in type 2 diabetes: What is the optimum Approach? .Clinical Diabetes 2008, vol 26, no :1, 8-13.

[15] Y.K.Kim, H.S.Seo, E.M.Lee et al. Association of small dense low- density lipoprotein in patients without metabolic syndrome. Journal of Human Hypertension, Oct 2011.doi: 10.1038/jhh.2011.86.

[16] Oya Demirci, Ahmet Semih et al. Serum lipids level assessed in early pregnancy and risk of pre-eclampsia. Journal of Obstretics and Gynaecology Research 2011, vol 37, Issue 10, 1427-1432.

[17] Amber V, Griffin B A et al. Influence of plasma lipid and LDL subfraction profile on the interaction between low density lipoprotein with human arterial wall proteoglycans. Atherosclerosis 1996: 124; 261-271.

[18] C. J. Packard et al. Triglyceride- rich lipoproteins and the generation of small dense low- density lipoprotein. Biochemical Society Transactions 2003, vol 31: part 5.

[19] Dreon D.M, Fernstrom H.A, Williams P T, Krauss R.M. A very low fat- diet is not with imoroved lipoprotein profiles in men with a predominance of large , low density lipoproteins. Ameican Journal of Clinical Nutrition, 1999: 69; 411-418.

[20] Tribble D L, Rizzo M, Chait A, Lewis D M, Blanche P J, Krauss R M. Enhanced oxidative susceptibility and reduced antioxidant content of metabolic precursors of small dense low density lipoproteins. Am J Med 2001; 110: 103-110.

[21] Patty W, Siri-Tarino, Paul T, Williams et al. Reversal of small dense LDL subclass phenotypes by normalization of adiposity. Obesity (2009), 17, 1768-1775.

[22] Frank M, Sacks, Hannia Campos. Low density lipoprotein size and cardiovascular disease: A reappraisal. The Journal of Clinical Endocrinology and metabolism, 2003: 88(10); 4525-4532.